REMARKS

I. Status of the Claims

Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100-109 were pending.

II. Requirements under 37 C.F.R. 1.497

The Assignee is filing herewith documents to satisfy the requirements of 37 C.F.R. § 1.497(d), which have not been submitted previously in the application. Submitted herewith are the statement of Mihai D. Azimoara under 37 C.F.R. § 1.497(d)(1) and the consent of the assignee under 37 C.F.R. § 1.497(d)(3). The processing fee under 37 C.F.R. § 1.17(i) as required under 37 C.F.R. § 1.497(d)(2) is authorized to be charged to Deposit Account 06-1050. No new oath or declaration is required under 37 C.F.R. §§ 1.497(d)(4) and (f). An oath meeting the requirements of 37 C.F.R. § 1.497(b) was submitted previously in the application.

III. Amendments

Claims 79 is amended by deleting "metabolic disorder" and inserting "obesity".

Claim 80 is amended by deleting the members of the Markush group other than "metabolic syndrome". The claim is also amended to depend from claim 1 instead of claim 79.

Claim 81 is amended to depend from claim 1 instead of claim 79. The amendment is not believed to alter the scope of this claim.

Claims 87-89 are cancelled.

Claim 90 is amended to depend from claim 1 instead of claim 85. The features of claims 84 and 85 are inserted into claim 90. The amendment is not believed to alter the scope of this claim.

Claims 110-115 are added and recite methods of treatment formerly recited in claim 80.

IV. Response to the Office Action

A. Response to the Objection to Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100-109.

Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100-109 were objected-to. The objection is moot as to claims 87-89, which have been cancelled, and is traversed as to the remaining claims.

The Office Action states the following:

Claims 1-5, 12-14, 16-66,73,74,78-85,87-92, and 100-109 are objected to because of the following informalities: In claim 1, the phrase "Formula (Ia) and pharmaceutically acceptable salts, hydrate, and solvates thereof" should be --Formula (Ia) or a pharmaceutically acceptable salt, hydrate, or solvate thereof--. In claims 73 and 74, the language "following compounds and pharmaceutically acceptable salts, hydrates, and solvates thereof" should be replaced with -following compounds, a pharmaceutically acceptable salt, hydrate, or solvate thereof--. In addition, the word "and" after the penultimate compound of claims 73 and 74 should be replaced with the word -or-- because claims 73 and 74 use the language "selected from", not the phrase "selected from the groups consisting of." Appropriate correction is required.

Applicants respectfully note that this objection has been raised previously and responded to in Applicants' papers filed on August 13, 2010 and December 13, 2010. Applicants respectfully note that neither the present nor previous Office Actions making this objection have provided any reasoning, or provided any citations to the MPEP or any legal authority, as to why the language objected-to is asserted to be "improper." Applicants respectfully submit a proper basis for an objection must be provided. Since no basis has been provided for the objection, Applicants ask once again that the objection be withdrawn.

Applicants respectfully disagree with the Office Action that the alternative language used in the present claim is "improper." When "selected from" is used, the conjunctive "and" should be used between the alternative elements (e.g. "selected from A, B **and** C"), because every one of the alternatives named (i.e. A, B **and** C) is available for selection. Thus it is perfectly proper to use the conjunctive. In the present case, the claim language makes the compounds of formula (I), salts thereof, as well as solvates and hydrates of such compounds and salts thereof available for selection and the use of the conjunctive "and" is therefore proper.

Withdrawal of the objection is respectfully requested.

B. Response to the Rejection of Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100-109 under the Enablement Requirement of 35 U.S.C. § 112, First Paragraph

Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100-109 were rejected under the Enablement Requirement of 35 U.S.C. § 112, first paragraph. The Office Action alleges that the specification does not reasonably provide enablement for making "any hydrates or solvates

within the scope of … claim 1." The objection is moot as to claims 87-89, which have been cancelled, and is traversed as to the remaining claims.

Applicants note that this rejection has also been made previously and Applicants traversed the rejection by providing a detailed response to the rejection, most recently in the response which was filed on December 13, 2010. The Office Action does not address a single one of Applicants' arguments.

Applicants respectfully point out that it is manifestly improper for the Office to maintain a rejection over Applicants' traversal without addressing the arguments made by Applicants in response. MPEP 707.07(h) explains that **"[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."** Applicants do not note in the Office Action any response addressing the substance of the arguments made in Applicants' response dated December 13, 2010. Applicants respectfully ask that if the present rejection is maintained, the Office fully address the remarks made below in response to the rejection.

In Applicants' paper filed on December 13, 2010, Applicants drew the Examiner's attention to two cases in which the Board of Patent Appeals and Interferences reversed examiners' rejections under the enablement requirement of 35 U.S.C. 112, first paragraph, on grounds that were very similar to the reasons that the present Office Action presents for rejecting the claims. Those cases were the **Final Decision of the Board of Patent Appeals and Interferences** in *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647 (Bd. Pat. App. & Int., Sept. 15, 2010) (available online at http://des.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd2009015302-09-15-2010-1) (non-precedential) and in *Ex Parte Germeyer*, Appeal No. 2010-005038, Appln. No. 10/891,554 (Bd. Pat. App. & Int., November 30, 2010) (available online at http://des.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd2010005038-12-01-2010-1) (non-precedential). Applicants noted, in particular, the apparent similarity between the rejection made in *Ex Parte Liu*, and the rejection made in the present application, and made the following request:

> If the enablement rejection is not to be withdrawn, Applicants request that the Examiner, in order to clarify the record as to the reasons why the rejection is

> being maintained, issue a further Office Action explaining what are the legally significant factual differences between the situation which was presented to the Board by Liu and the situation presented by the present application, and why the differences justify maintaining the enablement rejection in the present application. Applicants note that the same reasoning supported by the same references has been employed in the present Application as in the Application in Liu, where the rejection was found by the Board to have been made in error. Alternatively, if the Examiner cannot identify any legally significant differences justifying maintaining the rejection, Applicants invite the Examiner to explain what was the mistake the Examiner considers Administrative Patent Judges Scheiner, Green and Prats made in the Liu decision reversing Examiner Rao's identically reasoned rejection in Application 10/820,647.
>
> Applicants note that the Office Action dated May 13, 2010 was issued prior to the Board's decision in Liu, and was therefore prepared by Examiner Murray without the benefit of the insight the Liu decision provides as to the proper legal standards to be applied when considering enablement of compound claims that refer to a solvate, and the Board's view of the sufficiency of a rejection based on exactly the same reasoning as the one made in the present application.

Response to Petition Decision filed December 13, 2010.

Applicants note that in the present Office Action, the Office has failed to address the substance of Applicants' arguments regarding *Ex Parte Liu*. Applicants therefore respectfully reiterate the request set forth above that the Examiner explain legally significant factual differences between the situation which was presented to the Board in *Ex Parte Liu*, and why the differences justify maintaining the enablement rejection in the present application, or else to explain the mistake made by the Administrative Patent Judges in the *Liu* decision reversing the rejection in Application 10/820,647.

Turning to the explanation provided for the rejection, the Office claims that a *prima facie* case of insufficient enablement has been made based on the *Wands* factors. The requirements for a proper enablement rejection were explained as follows by the Board in *Ex Parte Liu*:

> "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." *In re Armbruster*, 512 F.2d 676, 678 (CCPA 1975). Instead, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).
>
> Thus, the threshold issue raised by this rejection is not whether Appellants have established that their Specification is enabling for making … solvates of the

> compound of Formula I. Rather, the issue is whether the Examiner has met his initial burden of providing a reasonable explanation as to why it isn't.

Ex Parte Liu, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 7 (Bd. Pat. App. & Int., Sept. 15, 2010).

The Office frames its reasoning in support of the rejection in terms of the *Wands* factors. Following a cursory treatment of each of the factors, the Office concludes:

> Considering the state of the art as discussed by the references above, particularly with regards to claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92, and 100-109 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Office Action dated January 19, 2011 at p. 4.

Applicants respectfully submit that the Office's treatment of the question of enablement of these claims is deficient considering that it is the Office's burden to prove that the person skilled in the art would be unable to practice the invention based on the disclosure provided in the specification. In discussing the *Wands* factors, the Office has ignored much of the evidence which is already of record, and even the evidence which was considered does not support the Office's conclusory finding of non-enablement.

Applicants will address the factors in the order that they were considered in the Office Action.

1. Nature of the Invention.

2. Breadth of the Claims.

The Office considers these factors together and states:

> The claims are drawn to a compound in which a pyrimidine ring is modified with a NH-C(=NR^8)NHR^7 at its 5-position and nitrogen-containing heterocyclic ring at its 4-position.Thus, the claims taken together with the specification imply that a pharmaceutically acceptable salt, hydrate, or a solvate of these compounds can be prepared.

Office Action dated January 19, 2011 at p. 3.

Nothing in the Office Action's consideration of these factors supports the Office's position that practicing the claimed invention would involve undue experimentation.

Applicants agree with the Office's assessment that the specification indicates that a hydrate or solvate can be prepared. The Office is reminded that this is *presumed true* unless the Office provides contrary evidence.

The claims are drawn to compounds of Formula (Ia) and pharmaceutically acceptable salts, hydrates and solvates thereof. The Office agrees that the person skilled in the art would be able to make compounds of Formula (Ia) and pharmaceutically acceptable salts thereof without undue experimentation. The other components of hydrates and solvates are water and common organic solvents. Thus claims are not unduly broad in any relevant aspect.

The nature of the invention is that it is drawn to pyrimidine compounds for medicinal use. Evidence of record shows that pyrimidine compounds are known to exist in the form of hydrates, and that hydrates are similar to solvates. There would be no reason to expect that hydrates or solvates not be formed with the presently claimed pyrimidine compounds.

In the relevant pharmaceutical art, the level of skill is high, and persons skilled in the art routinely engage in a substantial amount of experimentation such as routine screening of solvates, hydrates and polymorphs, in developing new drug products.

3. The State of the Art.

4. The Level of Predictability in the Art.

The Office again combines the consideration of these factors. The Office's entire discussion of them states:

> Hildesheim et al. (US 7056942, issued 6 June 2006) describe that solvate or hydrate formation/existence is unpredictable (column 2, line 60 to column 3, line 14).

Office Action dated January 19, 2011 at p. 3.

Applicants respectfully point out that Hildesheim does not provide the only evidence on record regarding the state and level of predictability in the art. Hildesheim describes the results of screening just one pharmaceutical compound for the existence crystalline forms, with the result that six such forms, including two hydrates and one solvate. Applicants respectfully submit that Hildesheim hardly supports the Office's position that the formation of hydrates and solvates of pharmaceutical compounds is particularly challenging.

The section of Hildesheim cited by the Office reads as follows:

> The existence and physical properties of different crystal forms can be determined by a variety of techniques such as X-ray diffraction spectroscopy, differential scanning calorimetry and infrared spectroscopy. Differences in the physical properties of different crystal forms result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly, polymorphs, hydrates and solvates are distinct solids sharing the same molecular formula yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family. The existence and physical properties of polymorphs, hydrates and solvates is unpredictable.
>
> One of the most important physical properties of a pharmaceutical compound which can form polymorphs, hydrates or solvates, is its solubility in aqueous solution, particularly the solubility in gastric juices of a patient. Other important properties relate to the ease of processing the form into pharmaceutical dosages, such as the tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet.

Although Hildesheim is consistent with the notion that it is difficult to predict in advance the existence and physical properties of hydrates and solvates obtainable from a particular compound, Hildesheim does not support the Office's position with regard to enablement because it shows the ease with which polymorphs, hydrates and solvates can be prepared empirically.

Hildesheim discusses that at least six different crystalline forms of a single compound – carvedilol – including two hydrates and a solvate - were formed just by recrystallizing carvedilol under various conditions. In Examples 1 and 2, Hildesheim describes that a hydrate form of carvedilol hydrochloride formed spontaneously just by forming carvedilol under neat conditions, partitioning the crude product between water and ethyl acetate, and acidifying the water to pH 5 with hydrochloric acid. Hildesheim also describes obtaining, without apparent difficulty, at least five other, different, crystalline forms of carvedilol, of which Forms III, IV and V were apparently novel.

Hildesheim found that Form III carvedilol was a hemihydrate (i.e. a hydrate with two molecules of carvedilol per molecule of water). See col. 10 lines 30-34. The material was formed simply by recrystallizing carvedilol from ethanol/water, methanol/water, pyridine/water, or hexane/IPA. See Examples 7-13 of Hildesheim. It is also noteworthy that the hemihydrate

form was formed under numerous different sets of conditions and hardly seems to have been challenging to discover.

Hildesheim found that Form V carvedilol was a mono-methyl ethyl ketone (MEK) solvate. See col. 10 lines 56-64. The material was formed by merely recrystallizing carvedilol from methyl ethyl ketone/hexane or by dissolving in methyl ethyl ketone followed by cooling. See Examples 14-15 of Hildesheim.

Hildesheim further describes that the new solid forms of carvedilol were easily characterized by powder X-ray diffraction (PXRD), their thermal profiles (differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)) and Karl Fisher analysis (KFA) (to detect water). See col. 9-11.

Hildesheim well supports enablement of the present claims as it provides a case study of the ease with which polymorphs, hydrates and solvates can be prepared empirically by using simple crystallization methods and characterized using techniques such as PXRD, DSC, TGA and KFA. Hildesheim is consistent with the other evidence of record in demonstrating that forming hydrates and solvates is easy to do empirically and as a result would not involve undue experimentation.

Applicants therefore respectfully do not agree that unpredictability is a factor that strongly weighs against a finding of enablement because the question of whether a solvate or hydrate forms can readily be answered empirically by employing routine screening methods. Predictability is only one of the factors to be considered in assessing enablement, unpredictability is not dispositive of the question of enablement. In the *Wands* case itself, making monoclonal antibodies was found to be *highly unpredictable* – much less predictable than forming hydrates and solvates – but the court found the enablement requirement to be met *as a matter of law*, because of the routine methods of screening involved. As in *Wands*, forming hydrates and solvates only requires routine and known methods of screening to be employed. Similarly the Board in *Ex Parte Liu* found that despite evidence that "it is difficult to predict whether a given compound will form a solvate or hydrate … solvates and hydrates are routinely produced and characterized empirically." *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647 at p. 8 (Bd. Pat. App. & Int., Sept. 15, 2010).

In addition to the Hilesheim reference, Applicants respectfully wish to bring, once again, to the Office's attention the other evidence of record with respect to the state of the art (of which the Office failed to take account in the present Office Action):

a. Vippagunta, et al., *Adv. Drug Delivery Reviews*, 2001, 48, 3-26.

This reference has been discussed extensively in the prosecution of the present application. The reference was cited by the Office to allegedly demonstrate that the claims were not enabled because of the unpredictability of solvate formation. The Board in *Liu*, however, disagreed with that interpretation of the reference. Although the Board did not dispute that "[the] Vippagunta reference[] show[s] that it is difficult to predict whether a given compound will form a solvate or hydrate" the Board found the reference provided "evidence that solvates and hydrates are routinely produced and characterized empirically." *Id.*

Hildesheim is consistent with Applicants' view as well as the Board's view of the Vippagunta reference.

Vippagunta also provides evidence that solvates and hydrates are ubiquitous among pharmaceutical compounds. On p. 15, Vippagunta indicates that it has been estimated that "approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates." Vippagunta also indicates that solvates are similar to hydrates. *See* Vippagunta p. 15 col. 1. Thus the person skilled in the art would recognize that a substantial percentage of pharmaceutically active substances are capable of forming hydrates and solvates. Thus it would be expected that employing such empirical methods to form and detect hydrates and solvates would yield a high rate of success:

Vippagunta also provides evidence that once hydrates and solvates are formed they can be analyzed by routine methods as described, for example, in Vippagunta, p. 18 to detect and quantify the presence of solvate molecules in the sample.

Vippagunta also provides evidence that demonstrates that the fact that the absence of any investigation into the existence of hydrate or solvate forms in the present application cannot be considered as an indication that such forms of the claimed compounds would not exist. It is not customary in early drug discovery to attempt to form hydrates or solvates or to analyze compounds to evaluate whether they are present as hydrates are solvates, as polymorphism and

solvate or hydrate formation is usually investigated in later stages of drug development as a drug candidate is being advanced towards regulatory approval. *See* Vippagunta pp 4-5.

b. Morisette, et al., *Adv. Drug Delivery Reviews*, 2004, 56, 275-300.

This reference describes that forming and characterizing hydrates and solvates is so routine that it is amenable to high throughput techniques such as high-throughput crystallization. Thus, formation of hydrates and solvates requires no more than routine screening.

c. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999.

This reference on pp. 202-209 describes typical procedures for making and identifying hydrates and solvates. Again, the reference supports Applicants' position that the methods for forming and characterizing hydrates and solvates are well known in the art and easy to perform. Thus, it would involve no more than routine screening to prepare and test for formation of hydrates and solvates empirically.

d. Sigma-Aldrich catalog entries for commercially available pyrimidine hydrates, namely 4,6-diamino-2-mercaptopyrimidine hydrate (catalog no. 125830); 2-amino-6-chloro-4-pyrimidinol hydrate (catalog no. 07460); 2-amino-6-hydroxy-2-mercaptopyrimidine monohydrate (catalog no. A57406); and 4,5-diamino-6-hydroxy-2-mercaptopyrimidine hemisulfate salt hydrate (392464).

Applicants have provided evidence that compounds having the same heterocyclic pyrimidine core structure as the presently claimed compounds are known to exist in the form of hydrates.

e. Abstract of Quesada, et al, *Acta Cryst*, 2003, C59, 102-104, documenting 2-amino-5-nitro-4,6-dipiperidinopyrimidinium hydrogensulfate monohydrate.

This reference provides further evidence that compounds having the same heterocyclic pyrimidine core structure as the presently claimed compounds are known to exist in the form of hydrates.

5. The Level of Skill in the Art.

The Office has stated that that persons of skill in the art "are those with level of skill of the authors of the references cited to support the examiner's position (MD's, PhD's, or those with advanced degrees and the requisite experience in solvate or hydrate formation)." The Office has previously stated that the person skilled in the art would be an "a chemist with a Ph.D. degree, and having several years of bench experience."

With respect to the aspect of the invention at issue, Applicants believe that the person skilled in the art might well be a formulator or solid state chemist rather than, for example, an MD. However, since the Office has characterized the level of skill in the art as being high, the Office does not dispute that the level of skill in the art is a factor supporting a conclusion of enablement.

6. Amount of guidance provided by the Applicants.

As Applicants have pointed out previously, the absence of specific guidance in the specification as to how to make hydrates and solvates, does not weigh heavily against a finding of enablement. The evidence cited in the prosecution of this application shows methods for making hydrates and solvates are well known and routine in the art and the law states that it is not necessary for "a patent specification to become a catalogue of existing technology", and "[a] patent specification need not teach, and preferably omits, what is well known in the art." MPEP 2182 (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986)). Furthermore, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007). Thus, the specification need not explain how to perform well-known methods for forming and screening for hydrates and solvates since the person skilled in art would be able to perform such methods readily without such guidance. The evidence cited with respect to the state of the art demonstrates that the methods for forming and characterizing hydrates and solvates are easy and routine.

7. Number of working examples.

The Specification does not explicitly describe any compounds as having been obtained in the form of a hydrate or solvate, but this should not be considered to weigh heavily against a finding that the claims are adequately enabled.

First, it is well established that there is no requirement for a "working" example for a claim to meet the requirements of the enablement requirement of 35 U.S.C. 112, first paragraph, when the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various hydrates and solvates of a particular organic molecule using the routine screening methods discussed above, no working example is necessary to enable the invention.

Secondly, the fact that the specification does not explicitly describe that any of the working examples were obtained in the form of hydrates or solvates does not provide any indication that compounds of the invention would not be capable of forming hydrates or solvates or exclude the possibility some of the compounds were obtained in the solvates.

The Experimental Section of the present application describes that the present Example compounds were generally purified by chromatography rather than recrystallization under the conditions which would typically form solvates. Crystallization methods such as those used in the Hildesheim reference cited by the Examiner for forming hydrates and solvates were not generally employed. Thus, there is no evidence that preparation of the Examples was formed under conditions favorable for hydrate or solvate formation.

In addition, the compounds of the Examples were not analyzed using methods which would have detected the presence of a hydrate or solvate. The specification clearly explains that samples for NMR and mass spectrometry were analyzed in solution not in the solid state. See Specification p. 127. Hydrates and solvates, by definition, only exist in the solid state. Thus, it is quite possible that some of the Example compounds might have been formed in the form of a hydrate or solvate without this fact being detected.

Thus, the fact that examples of hydrate or solvate formation were not described in the Specification does not show that such forms of the claimed compounds are difficult to form, or even that they were not formed.

The Board in *Ex Parte Liu* also found the Examiner's reasoning that solvates were not enabled because of a lack of working examples to be unconvincing because the "conditions … were unfavorable for solvate formation and therefore not indicative of the nonexistence of solvates." *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 9 (Bd. Pat. App. & Int., Sept. 15, 2010). In the present case Applicants have pointed out that not only were the conditions unfavorable for hydrate or solvate formation, but that no attempt was made to detect whether the compounds were present in the form of hydrates or solvates. The Examiner has presented no contrary evidence showing that the conditions would have been favorable for hydrate or solvate formation or that the analytical methods used by Applicants would have detected a hydrate or solvate, if present.

8. The Amount of Experimentation Needed to Make the Invention.

Applicants respectfully submit that, in view of the foregoing factors, the amount of experimentation required to carry out the claimed invention with the guidance would be by no means undue. There is no dispute that the specification adequately describes how to make compounds of Formula (Ia) without undue experimentation. Since the evidence cited by the Applicants shows that hydrates and solvates of pharmaceutically active compounds are ubiquitous and methods of preparing and screening for hydrates and solvates are straightforward and routine in the extreme, all that would be required to make hydrates and solvates of compounds of Formula (Ia) and salts thereof would be to apply the routine methods of making and screening for hydrates and solvates.

The situation presented in the present case remains exactly analogous to the situation, with respect to enablement of hydrates, as was presented to the Board in *Ex Parte Liu*. Here, as in Ex Parte Liu, "the Examiner has overemphasized the importance of working examples, and given "too little credit to the abilities of a person having ordinary skill in the art." *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 8 (Bd. Pat. App. & Int., Sept. 15, 2010).

In view of all the foregoing remarks, the Applicants respectfully request that the rejection of claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100-109 under the enablement requirement

of 35 U.S.C. § 112, first paragraph based on the recitation of hydrates and solvates in the claims be withdrawn.

C. Response to the Rejection of Claims 79-81, 83-85, 87-89 and 91 under the Enablement Requirement of 35 U.S.C. § 112, First Paragraph

Claims 79-81, 83-85, 87-89 and 91 were rejected under the Enablement Requirement of 35 U.S.C. § 112, first paragraph. The Office Action acknowledges that the claims are adequately enabled for methods of treating type II diabetes and obesity, but alleges that the specification does not reasonably provide enablement for making "treatment of the scope of disorders claimed." The objection is moot as to claims 87-89, which have been cancelled, and is traversed as to the remaining claims.

Applicants respectfully point out that the Office, in making the rejection, has again failed to take account of the burden which must be met before an enablement rejection. The Examiner notes that the specification describes that the compounds of the present application can treat the disorders recited in the rejected claims. Applicants agree, and respectfully point out that, in view of the presumption of enablement, the statements in the specification are presumed to be true unless the Office meets it burden of providing that the contested statements are untrue.

Applicants respectfully submit that the Office has provided no basis for its contention that the claims directed to methods of treatment are not adequately enabled in the specification. The Office cites Fyfe, which the Office acknowledges demonstrates that the specification is, in fact, enabling for the treatment of obesity and type 2 diabetes. While the Office Action states that Fyfe does not describe that RUP3 modulates any other disorders, the Office Action also does not claim that Fyfe claims that RUP3 in fact does not modulate the other disorders. Thus, Fyfe does not support the Office's position in any way. Similarly the WebMD website's claim that "currently there is no way to prevent type 1 diabetes" does not demonstrate that the presently claimed compounds could not achieve such prevention. In fact, the WebMD website acknowledges the possibility of such prevention noting that "ongoing studies are exploring ways to prevent diabetes" thereby acknowledging that prevention of type 1 diabetes can be achieved.

Applicants also respectfully point out that the remarks set forth in the Office Action do not support the rejections made. For example, the Office has acknowledged that the claims are

enabling for treatment of type II diabetes and obesity, while yet rejecting claim 81 (which recites treatment of type II diabetes) and claim 90 (which recites controlling or reducing weight gain). Thus, the rejections are inconsistent even with the positions that the Office has taken with respect to the issue of enablement.

In order to expedite prosecution, Applicants have amended the claims to take account of the Office's remarks. Applicants respectfully submit upon consideration of the *Wands* factors, the present versions corresponding to the rejected claims should be found enabled: Applicants address those factors below in the order in which they were considered in the Office Action.

1. Nature of the Invention.

2. Breadth of the Claims.

The Office considers these factors together and states:

> The claims are drawn to a compound in which a pyrimidine ring is modified with a NH-C(=NR^8)NHR^7 at its 5-position and nitrogen-containing heterocyclic ring at its 4-position. Thus, the claims taken together with the specification imply that a compound of the instant application can treat one or more of the disorder recited in claims 79-81,83-85,87-89, and 91.

Office Action dated January 19, 2011 at pp. 4-5.

Nothing in the Office Action's consideration of these factors supports the Office's position that practicing the claimed invention would involve undue experimentation.

Applicants respectfully point out that claims 82-84, 91 and 92 do not, as the Office Action alleges, recite treatment of a disease, but instead recite modulating a RUP3 receptor. Thus it is not seen how the Office Action's assertions regarding treatment of disease in any way impact the question of enablement of these claims. The Office has provided no explanation whatsoever as to why the use of the claimed compounds to modulate a RUP3 receptor should be considered to involve undue experimentation.

Applicants agree with the Office's assessment that the specification indicates that the claimed compounds would be useful for treating the disorders of claims 79-81 and 91, as well as those of new claims 110-115. The Office is reminded that enablement of these methods is *presumed* unless the Office provides contrary evidence. No such contrary evidence has been presented with respect to any of the diseases recited in claims 79-81, 91 or 110-115.

Thus, there is nothing with respect to the nature of the invention or the breadth of the claims that supports the Office's assertion that the specification is not enabling for the methods recited in claims 79-81, 82-84 or 91, or the methods recited in new claims 110-115.

3. The State of the Art.

The Examiner cites Fyfe, *Expert Opinion in Drug Discovery*, **2008**, 3(4) 403-413 as the only evidence regarding the state of the art. However, while the Office Action cites Fyfe as supporting enablement of the claims for treating type II diabetes and obesity, the Office Action only alleges that Fyfe fails to indicate that RUP3 modulators would be useful for treating the other diseases claimed.

Applicants respectfully point out that in view of the presumption of enablement to which the claims are entitled, the mere absence of support for enablement of the claims in one reference (which Applicants do not acknowledge) cannot be considered in any way to meet the Office's burden of providing a basis for the rejection.

In addition, the Office's evidence with regard to type I diabetes, although it again does not support the Office's position, is moot in view of the fact that the claims as presently amended do not recite treatment of type I diabetes.

Applicant notes that the Office Action acknowledges that the specification provides adequate enablement of the treatment of obesity and diabetes. Based on this acknowledgement, the Office should withdraw the rejection of claims 79-81, 83-85 and 91 and also acknowledge that claims 110-115 are also adequately enabled.

Claim 79 has been amended to recite treatment of obesity. Based on the Office's acknowledgement that treating obesity with the claimed compounds is adequately enabled, the Office should withdraw the rejection of claim 79. The Office should also withdraw the rejection of claim 90, which recites a method of modulating the RUP3 receptor which controls or reduces weight gain in an individual. The Office has acknowledged that the claimed compounds modulate the RUP3 receptor, and that the specification provides adequate enablement for treating obesity, treatment of which would necessarily require controlling or reducing weight gain of an individual with obesity. The Fyfe reference cited by the Office in support of the

rejection describes that RUP3 (GPR119) agonists modulate food intake and body weight. See pp. 409-410 of Fyfe.

Claim 81 recites treatment of type II diabetes. Based on the Office's acknowledgement that treating type II diabetes with the claimed compounds is adequately enabled, the Office should withdraw the rejection of claim 81.

Claim 110 recites treatment of insulin resistance. Based on the Office's acknowledgement that treating type II diabetes with the claimed compounds is adequately enabled, the Office should acknowledge enablement of treating insulin resistance since insulin resistance is characteristic of type 2 diabetes. See Mayo Clinic Staff, "Type 2 diabetes" (available online at http://www.mayoclinic.com/health/type-2-diabetes/DS00585) which states "Type 2 diabetes develops when the body becomes *resistant to insulin*..." (emphasis added). Thus, methods of treating insulin resistance are also clearly enabled. Fyfe also notes that "[t]ype 2 diabetes is characterised by abnormalities ... insulin resistance." See Fyfe p. 403.

Claim 111 recites treatment of inadequate glucose tolerance. Based on the Office's acknowledgement that treating type II diabetes with the claimed compounds is adequately enabled, the Office should acknowledge enablement of treating insulin resistance since inadequate glucose tolerance is again characteristic of type 2 diabetes. Inadequate or impaired glucose tolerance is an early symptom of type II diabetes. See Rao, et al. Impaired Glucose Tolerance and Impaired Fasting Glucose, *Am. Fam. Physician*, **2004**, 69(8) 1961-1968. Fyfe in fact describes that RUP3 (GPR119) agonists are effective for controlling inadequate glucose tolerance, noting that "GPRI19 agonists can suppress glucose excursions when administered before glucose tolerance tests." Fyfe p. 407.

Claims 112-115 recite treatment of hyperglycemia, hyperlipidemia, hypertriglyceridemia and hypercholesterolemia. Based on the Office's acknowledgement that treating type II diabetes with the claimed compounds is adequately enabled, the Office should acknowledge enablement of treating insulin resistance because hyperglycemia and hyperlipidemia (which includes hypertriglyceridemia and hypercholesterolemia) are serious conditions closely associated with or caused by diabetes. Treatment of diabetes would necessarily include treatment of the symptoms of diabetes, including hyperglycemia, and include treatment of the conditions in which diabetes is a contributing factor such as hyperlipidemia. The treatment of diabetes would be expected to

also treat the symptoms of diabetes, including hyperglycemia and hyperlipidemia. Fyfe discusses "antihyperglycemic actions" of RUP3 (GPR119) agonists on p. 407.

The enclosed documents are provided as additional evidence that hyperglycemia and hyperlipidemia are closely connected with and are symptoms of type II diabetes:

- American Diabetes Association, "Hyperglycemia (high blood glucose)" (available online at http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hyperglycemia.html (describing hyperglycemia as a symptom of diabetes).
- Kreisberg et al., "Hormones & You Patient Information Page: Hyperlipidemia (High Blood Fat" J. Clin. Endocrinol., 2005, 90, 0 (available online at http://jcem.endojournals.org/cgi/reprint/90/3/0.pdf) (stating that "[Hyperlipidemia] can … be related to a hormonal disease such as diabetes mellitus"). The reference notes that the blood fats which may be elevated in hyperlipidemia include cholesterol (i.e. hypercholesterolemia) and triglycerides (i.e. hypertriglyceridemia).
- Society for Vascular Surgery, "Vascular Web – Hyperlipidemia" (available online at https://www.vascularweb.org/vascularhealth/Pages/Hyperlipidemia.aspx) (page 2, "Conditions that cause hyperlipidemia include diabetes". The reference notes that "[h]yperlipidemia includes several conditions, but it usually means that you have high cholesterol and high triglyceride levels."

Enablement of treating hyperlipidemia, including hypertriglyceridemia and hypercholesterolemia, should also be acknowledged based on the Office's acknowledgment that the claims are enabled for treating obesity since hyperlipidemia, including hypertriglyceridemia and hypercholesterolemia are associated with obesity. For example, Lai et al. " Association Between Obesity and Hyperlipidemia Among Children", *Yale J. Biol. Med.*, **2001**, *74*, 205-210 found that "[o]besity was associated with hyperlipidemia in children" (see Abstract).

Finally, claim 80 recites treatment of metabolic syndrome. Since the Examiner asserts that the symptoms of metabolic syndrome include, among other things type II diabetes and other glucose and lipid metabolism disorders, the Office should also acknowledge that treatment of metabolic syndrome is enabled. Since the Office must acknowledge that the specification adequately enables use of the claimed compounds for treating significant components of

metabolic syndrome, including type II diabetes and insulin resistance, the Office should also acknowledge that the claims are adequately enabled for treating metabolic syndrome.

4. The Level of Predictability in the Art.

Although the conclusion of the Office Action's remarks cite "high unpredictability in the art as evidenced therein," Applicants respectfully point out that the Office Action actually cites no evidence whatsoever to back up the Office's conclusory remarks regarding supposedly "high unpredictability" referred to in the Office Action. Other than the conclusory remark regarding alleged "high unpredictability", the Office Action does not provide any evidence or relevant discussion of this factor. There is therefore no evidence or reasoning of record that supports unpredictability in the art as a factor tending to support the rejection of the claims for lack of sufficient enablement. Applicants also point out that, as the *Wands* case itself demonstrated, the absence of absolute predictability is not, in any case, determinative of the question of enablement.

5. The Level of Skill in the Art.

The Office has stated that persons of skill in the art "are those with level of skill of the authors of the references cited to support the examiner's position (MD's, PhD's, or those with advanced degrees and the requisite experience in solvate or hydrate formation)." Since the Office has characterized the level of skill in the art as being high, the Office apparently does not dispute that the level of skill in the art is a factor supporting a conclusion that the specification would adequately enable the person skilled in the art to carry out the claimed methods.

6. Amount of guidance provided by the Applicants.

7. Number of working examples.

The Office Action acknowledges that "[t]he specification has provided guidance for treatment of type II diabetes and obesity" but alleges that "the specification does not provide guidance for the scope of disorders claimed." Office Action dated January 19, 2011 at p. 5.

Applicants appreciate the Office's acknowledgement that the specification provides adequate guidance for treatment of obesity and type II diabetes. Applicants respectfully disagree that the specification does not provide adequate guidance to enable the other claimed methods.

Claims 82-84, 91 and 92 recite methods of modulating a RUP3 receptor. Applicants respectfully submit that the specification provides ample guidance on how to use the claimed compounds to modulate a RUP3 receptor. For example, the specification describes the structures of compounds that are effective to modulate RUP3, including numerous embodiments thereof, and how to make such compounds and numerous working examples of such compounds. See, e.g. pp. 19-90 and 127-212 of the Specification. The specification describes how to make formulations of the compounds for administration to modulate the RUP3 receptor in vivo. See, e.g., pp. 103-108. The Specification also describes assays that can be used to identify the most effective RUP3 modulators. See, e.g., pp. 113-118, 125-126. Assays involving modulating RUP3 in vitro are illustrated. See, e.g. pp. 121-122. In addition, in vivo assays are described as well as data obtained in such an assay. See, e.g., pp. 122-212 and Figures 5A and 5B. Assay data for representative compounds are provided. See, e.g., p. 212. Thus, there is extensive guidance in the specification on modulating RUP3 with the claimed compounds.

The also provides extensive guidance on how to use the claimed compounds to treat obesity and type II diabetes, as the Office acknowledges. Based on the art-recognized association between obesity and type II diabetes and the other disorders for which methods of treatment are claimed, including impaired glucose metabolism (including inadequate glucose tolerance and hyperglycemia) and impaired lipid metabolism (including hyperlipidemia, including hypertriglyceridemia and hypercholesterolemia), as well as the metabolic syndrome which includes such conditions, the person skilled in the art would recognize that guidance for treating these conditions is also adequate. It should be noted, in particular, that the specification provides in vivo results showing the effect of the claimed compounds on glucose homeostasis. See, e.g., Example 6, pp. 122-123 and Figures 5A and 5B. Since the compounds were effective in a glucose intolerance test and to lower blood glucose in vivo, the effectiveness of the claimed compounds for treating inadequate glucose tolerance and hyperglycemia, in particular, should be apparent.

Applicants therefore respectfully submit that the use of the claimed compounds for carrying out the claimed methods is well enabled by the specification.

8. The Amount of Experimentation Needed to Make the Invention.

Applicants respectfully submit that, in view of the foregoing factors, the amount of experimentation required to carry out the claimed invention with the guidance would be by no means undue. There is no dispute that the specification adequately describes how to use the claimed compounds for treating obesity and type II diabetes. Since the association between obesity and type II diabetes and the other disorders for which methods of treatment are claimed, including impaired glucose metabolism (including inadequate glucose tolerance and hyperglycemia) and impaired lipid metabolism (including hyperlipidemia, including hypertriglyceridemia and hypercholesterolemia), as well as the metabolic syndrome which includes such conditions is recognized in the art, it would not involve undue experimentation to treat such conditions as well. The specification also provides extensive guidance on how to modulate the RUP3 receptor, both in vitro and in vivo, and it would therefore also not involve undue experimentation to carry out the claimed methods of modulating the RUP3 receptor either.

Based on the foregoing, withdrawal of the rejections of claims 79-81, 83-85 and 91 is respectfully requested. It is also requested that the Office acknowledge enablement of the methods claimed in claims 110-115.

D. Rejection of Claims 80 and 88 under 35 U.S.C. § 112, Second Paragraph

Claims 80 and 88 were rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. The Office Action alleges the claims are indefinite because the claims contain a "group within a group" because the concept of metabolic syndrome allegedly "includes type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesteremia, dyslipidemia and syndrome X." Office Action p. 6.

Applicants respectfully point out that the Office Action does not explain why the fact that elements of a Markush Group might overlap in scope would make it unclear what a claim is intended to cover. Applicants cannot find any reference in 35 U.S.C. 112, second paragraph prohibiting claiming a "group within a group" and Applicants also cannot find any authorization for such a rejection in the MPEP. In fact the MPEP specifically points out that Markush elements are permitted to overlap in scope. MPEP 2173.05(h) states:

> [T]he double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims. … The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though "halogen" is generic to "chloro."

There is, therefore, no basis for the Office Action's "group within a group" rejection as the MPEP specifically acknowledges that a "group within a group" is permitted.

Applicants respectfully submit, however, that the rejection is moot in view of the amendments deleting the Markush elements other than "metabolic syndrome" in claim 80 (so that "metabolic syndrome" is no longer, as the Office Action puts it, a "group within a group" and cancelling claim 88.

Withdrawal of this rejection is requested.

E. Obviousness-Type Double Patenting

Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100 were provisionally rejected for double patenting over claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100 of co-pending Application No. 12/945,712. The Office Action alleges that the presently pending claims are not distinct from the claims of Application No. 12/945,712. The rejection is moot as to claims 87-89, which have been cancelled and is respectfully traversed as to the remaining claims.

Applicants respectfully point out that since the double patenting rejection has been made only provisionally, Applicants need not address the provisional rejection until such time as the rejection matures into a real rejection. Applicants respectfully disagree with the grounds of rejection on the basis that the claims of the present application would not represent an unjustified extension of the patent protection that would be granted by the later-filed application (if the later filed application issues as a patent) because the present application is the earlier-filed application. Applicants respectfully point out that, according to MPEP 804, once all the rejections have been overcome in an earlier filed application, that Application should be allowed to proceed to issue without requiring a Terminal Disclaimer. MPEP 804 explains:

> [i]f a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending

> applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. ...
>
> If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.

By virtue of the remarks set forth above, Applicants respectfully submit that since all the rejections of record have been overcome based on present amendments and response, the obviousness-type double patenting rejection should also be withdrawn based on the guidance set forth in MPEP 804.

Withdrawal of this rejection is therefore also requested.

If required, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline for response. The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050 quoting Attorney's Docket No. 20750-0007US1 / 034.US5.PCT.

Respectfully submitted,

Date: April 15, 2011

Eifion Phillips, J.D., D.Phil.
Reg. No. 55,538

Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, MN 55440-1022
Telephone: (302) 652-5070
Facsimile: (877) 769-7945